with increases in cigarette smoking. Ex-cigarette smokers tended to have results similar to those of nonsmokers. The authors found that the mebrane component did not show any consistent change with increased current cigarette smoking, whereas the volume of blood in the lung capillaries decreased markedly with increased cigarette consumption, and slightly with age. The value of this vascular component in male nonsmokers was 75.5. This decreased to 49.1 in males who smoked 25 or more cigarettes a day ($P<0.01$). The figures for women were 77.2 and 50.7 for nonsmokers and smokers, respectively ($P<0.05$).

Acetaldehyde is found in cigarette smoke and is a known ciliatoxic agent. The single-breath retention of acetaldehyde vapor by the respiratory tract of human subjects was measured by Egle (*16*) who found a direct relationship between the volume inhaled and the percent taken up. Up to 90 percent of the inhaled acetaldehyde was removed in a single breath.

Stanescu (*79*) studied the single-breath oxygen test in 38 male smokers and 68 male nonsmokers who were in excellent health. A significant difference ($P<0.001$) in the slope of the nitrogen gradient between smokers and nonsmokers was found.

Teculescu (*83*) performed single-breath determinations of total lung capacity in 89 males aged 19 through 67 who had normal chest X-rays and no history of respiratory disease. No significant differences were found with age or smoking habits.

Pulmonary Clearance

Studies in Man

Tracheobronchial clearance rates were studied in nine pairs of monozygotic and nine pairs of dizygotic twins by Camner, et al. (*12*). A test aerosol of radioactively tagged teflon particles 6 to 7 microns in diameter was inhaled and external measurements of radioactivity in the lungs were made. The clearance patterns within pairs of monozygotic twins were similar, more so than clearance patterns within pairs of dizygotic twins, indicating that tracheobronchial clearance rates may to some extent be constitutionally determined. Only one individual had been a regular cigarette smoker.

Camner and Philipson (*10*) also studied tracheobronchial clearance in smoking-discordant twins, using the same techniques as in the previous study; 10 pairs of monozygotic twins discordant with regard to cigarette smoking were studied. All the smokers had used 10 to 20 cigarettes a day for more than 20 years. Tracheobronchial clearance was, on the average, significantly ($P<0.02$) slower in the smokers

than in the nonsmokers. Although the basic rate of mucociliary transport may be constitutionally determined, it is evident that cigarette-smoking decreases the effectiveness of this physiologic mechanism.

The regional deposition of inhaled aerosols in man was studied by Lippmann, et al. (*50*), who used a monodisperse ferric oxide aerosol tagged with a radioisotope. Particles were deposited in the pharynx, trachea, bronchi, and alveoli. Measurements were made in 65 adults including 14 nonsmokers, 29 current cigarette smokers, six elderly bronchitic patients, and one young asthmatic. Larger particles were deposited in the upper airways by turbulent precipitation with only the small particles of one to five micron size reaching the lower airways. The cigarette smokers, bronchitics, and the asthmatic had a higher proportion of particles deposited in the tracheobronchial area than nonsmokers. As a result, fewer particles reached the alveoli in these patients. These findings may be the result of a decrease in the diameter of the small bronchioles due to inflammation, mucus, or bronchoconstriction.

Albert, et al. (*3*) studied the effects of cigarette smoking on the kinetics of bronchial clearance in a group of volunteers most of whom also participated in the previous study. A two-phase clearance pattern was described for many subjects. The first, a short, rapid clearance phase, was completed within a few hours and probably represented clearance of the upper airways. The second phase varied in duration from a few hours to 1 day and represented clearance of particles deposited in the distal portions of the bronchial tree. The average clearance time was 126 minutes in 18 nonsmokers, 170 minutes in 19 of the smokers, and 238 minutes in the six patients with bronchitis, most of whom had been heavy cigarette smokers for many years. Much variation in clearance rates was found among smokers. Cigarette smoking resulted in diminished pulmonary clearance in the upper airways first. As a result, mucus cleared from the lower airways accumulated in the larger airways where stasis occurred. In severe cases, stasis was more generalized throughout the bronchial tree.

Sanchis, et al. (*74*) also studied lung clearance mechanisms in nine adult females who had smoked more than 15 cigarettes a day for more than 5 years and who had no evidence of bronchitis or respiratory disease. A group of nonsmoking females matched for age served as controls. A heterodisperse aerosol of I^{131} tagged human albumin was inhaled by the volunteers, and measurements of radioactivity were made over three crescentic areas of the right lung which corresponded to large ciliated airways, intermediate bronchi, and nonciliated peripheral airways and alveoli. Cigarette smokers exhibited a slowing of the rapid clearance phase of the large ciliated airways and also a relative acceleration in the second clearance phase resulting in an accumulation of activity at the hilar area. Comparing the clearance among

smokers and nonsmokers, the authors found that the nonsmokers retained twice as much activity in the lung at the end of 24 hours as did the smokers. This finding resulted from the deposition of much more of the aerosol distal to the ciliated airways in nonsmokers than in smokers suggesting that seemingly healthy smokers may have obstruction of the small airways.

Camner, et al. (*11*) examined the short-term effects of heavy cigarette smoking on mucocilary transport using the same methods as in his previous studies (*10*, *12*). The subjects were 13 men aged 27 to 38 who had been habitual smokers for several years. Baseline clearance rates were measured after refraining from cigarette smoking for 1 hour. The subjects then repeated the test but were instructed to "chain smoke" by inhaling the smoke as deeply and as frequently as possible, but without coughing. Subjects smoked much more intensely than under normal circumstances. The speed of mucocilary transport was significantly higher during intensive cigarette smoking than when they were not smoking ($P<0.01$). These results differ from the results of other investigators. The effect of the deep regular inhalation patterns used during the period of heavy smoking on clearance rates remains uncertain.

Studies in Animals

Rylander (*73*) studied the effect of cigarette smoke on the clearance of radioactively tagged particles and viable bacteria in the lungs of 114 experimental and control guinea pigs. The clearance of particles measures mucus transport whereas the clearance of viable bacteria is a partial indicator of phagocytic activity. Inhalation of smoke from cigarettes with varying levels of "tar" resulted in similar decreases in both the mechanical and bactericidal clearance. In each case, the mechanical clearance appeared to be affected earlier than the bactericidal clearance. When phenylmethyloxadiazole (PMO) was added to the tobacco, neither the mechanical nor bactericidal clearance was affected by cigarette smoke.

Dalhamn and Rylander (*14*) also reported that phenylvinyloxadiazole (PVO) and phenylmethyloxadiazole (PMO), when added to tobacco, were effective in reducing the ciliotoxic effects of cigarette smoke in in vivo cat trachea preparations.

Phagocytosis

Rylander (*72*) studied the effect of acute and chronic exposure to cigarette smoke on the number of alveolar macrophages in the guinea pig. Acute exposure to the smoke of five or more cigarettes, resulted in

a significant ($P<0.05$) reduction in the number of alveolar macrophages. With more prolonged exposure to cigarette smoke, an increase occurred in the number of alveolar macrophages over control values.

The effect of nitrogen dioxide (NO_2), a compound found in cigarette smoke, on alveolar macrophages in rabbits was studied by Acton and Myrvik (*1*). Phagocytic activity and virus-induced resistance to rabbitpox virus were suppressed by exposure to 15 p.p.m. of NO_2 over a 3-hour period.

Bacterial and Mycological Studies

The prevalence of fungi in the throat was examined by Martin, et al. (*56*) in a population of 365 male and 103 female European patients in South Africa who were hospitalized for a variety of conditions. Throat swabs were taken shortly after admission and plated on appropriate culture media. The yeasts isolated were Rhodotorula mucilaginosa, Torulopsis glabrata, and seven species of Candida. A seasonal variation in prevalence was noted with a decline in the winter and with peaks in the spring and summer. Smokers of more than 30 cigarettes a day had a higher prevalence of pharyngeal fungi than nonsmokers or those smoking less than this amount. No effect of age or disease category on the prevalence of pharyngeal fungi was found.

The bacterial flora in respiratory tree secretions obtained at bronchoscopy from 207 patients with chronic lung disease and 48 controls were characterized by Dobisova, et al. in a study from Germany (*15*). No relationship was found between smoking or severity of respiratory symptoms and the composition of the bacterial flora. They also reported that smokers comprised 84.6 percent of those with chronic cough but only 58.3 percent of the controls.

The effects of nitrogen dioxide and cigarette smoke on the retention of inhaled bacteria were investigated by Henry, et al. (*32*). Male golden hamsters were exposed to an aerosol of Klebsiella pneumoniae following exposure to NO_2 and/or cigarette smoke. A control group was exposed to the pathogen without pretreatment. Acute exposure to either NO_2 or cigarette smoke resulted in an increased mortality and decreased survival time from Klebsiella infections. Exposure to both NO_2 and cigarette smoke reduced the rate of clearance of viable bacteria from the lungs to a greater extent than exposure to either substance alone. The increase in lethal effects of Klebsiella exposure may have resulted from inhibition of the mucociliary transport system or reduction of phagocytic capacity of the alveolar macrophages.

Finley and Ladman (*20*) measured pulmonary surfactant in cigarette smokers and nonsmokers. The surfactant was recovered after endobronchial lavage. The lipid content of surfactant in smokers and nonsmokers was qualitatively similar; however smokers had on the average only 14.3 percent of the surfactant levels found in nonsmokers. Their levels of surfactant returned promptly to levels found in nonsmokers following cessation of smoking. Cigarette smoking may reduce the quantity of surface active material lining the alveolar walls through either decreased production, an increased removal, or a dilution with mucus from the airways.

Summary of Recent Nonneoplastic Bronchopulmonary Findings

In addition to the summary presented in the introduction of this chapter, based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field:

1. Epidemiological and clinical studies from several countries confirm that cigarette smoking by both men and women is associated with an increased prevalence of respiratory symptoms and decreased pulmonary function compared to nonsmokers.
2. The regular use of filter cigarettes is associated with less cough and sputum production compared with the regular use of nonfilter cigarettes.
3. Cigarette smoking in combination with certain occupational exposures is associated with a higher prevalence of respiratory symptoms and COPD than is observed with either cigarette smoking or occupational exposure alone. Byssinosis is found more frequently in cotton mill employees who smoke cigarettes than in nonsmoking workers.
4. Recent autopsy studies confirm that pulmonary emphysema is much more frequent and severe in cigarette smokers than in nonsmokers.
5. Several recent investigations have confirmed that cigarette smoking exerts adverse effects on pulmonary clearance and macrophage function.

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CHAPTER 3

Cancer

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Introduction

This introduction is a brief summary of the major relationships between smoking and cancer which have been established in previous reports on the health consequences of smoking (*91*, *92*, *93*, *94*, *95*, *96*).

Cigarette smoking has been clearly identified as the major cause of lung cancer in the United States. This conclusion is based on detailed epidemiological, clinical, autopsy, and experimental data which have accumulated over a period of more than 20 years. For both men and women, the risk of developing lung cancer is directly related to total exposure to cigarette smoke as measured by the number of cigarettes smoked per day, the total lifetime number of cigarettes smoked, the duration of smoking in years, the age at initiation of smoking, the depth of inhalation of tobacco smoke, and the "tar" and nicotine levels in the cigarettes smoked. Lung cancer death rates, however, are lower for women than they are for men, a finding due, in part, to a difference in exposure. Women smokers use fewer cigarettes a day, choose filtered cigarettes with lower "tar" and nicotine values, and also tend to inhale less. However, even when women experience comparable levels of exposure to cigarette smoke as men, their mortality rates for lung cancer still remain somewhat lower.

Those who stop smoking experience a decline in the risk of developing lung cancer relative to continuing smokers. The air pollution commonly found in an urban setting appears to result in elevated lung cancer death rates; however, this effect is relatively small compared to the overriding effect of cigarette smoking.

Certain occupational exposures have been found to be associated with an increased risk of dying from lung cancer. Cigarette smoking interacts with many of these exposures to produce much higher death rates from lung cancer than would result from one exposure alone. Interacting exposure factors may be experienced simultaneously or at different times. The uranium mining and asbestos industries are examples of occupations in which this interaction occurs.

The bronchial epithelium of smokers often shows premalignant changes including squamous metaplasia, atypical squamous metaplasia, and carcinoma in situ.

Pipe and/or cigar smokers experience a risk of developing lung cancer that is higher than the risk of nonsmokers; however, it remains

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significantly lower than the risk of cigarette smokers. A more complete discussion of the risks from pipe and cigar smoking is found in another chapter of this report.

Epidemiological, experimental, and autopsy data have demonstrated that cigarette smoking is a significant factor in the development of cancer of the larynx, oral cavity, esophagus, and urinary bladder. B-naphthylamine, a carcinogen known to cause cancer of the urinary bladder in humans, has been identified in cigarette smoke. There is also an association between cigarette smoking and cancer of the pancreas. Experimental studies with animals in which cigarette smoke or one of its constituent compounds is administered in a variety of assays have confirmed the presence of complete carcinogens, cocarcinogens such as tumor initiators and tumor promoters, and tumor accelerators in cigarette smoke.

Recently, additional epidemiological, autopsy, and experimental studies have added to our understanding of these relationships.

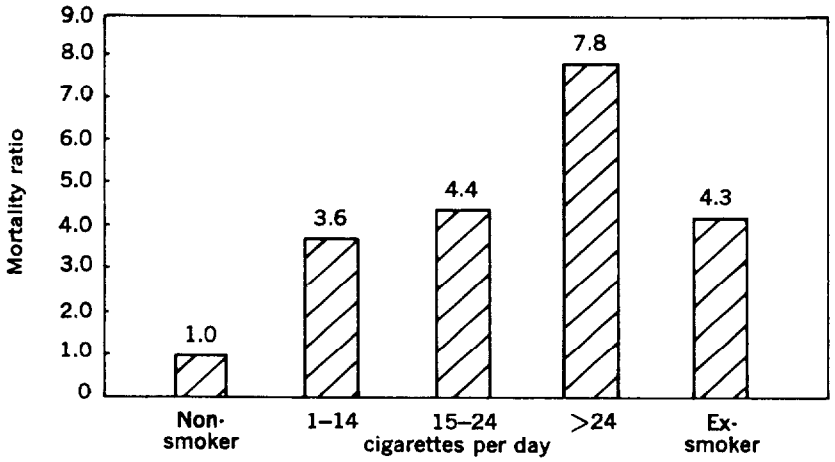
Lung Cancer

Epidemiological Studies

An ongoing prospective epidemiological study conducted in Japan provides a unique opportunity to examine the relationship of cigarette smoking to death rates in a population with genetic, dietary, and other cultural differences from previously examined Western populations. Hirayama (*37*) has now reported 5-year followup data on 265,118 men and women aged 40 years and older. This represented 91 to 99 percent of the total population in the area of the 29 health districts where the study was conducted. A total of 11,858 deaths occurred during the 5-year period which included a total of 1,269,382 person-years of observation. Both men and women who smoked cigarettes experienced higher death rates from lung cancer than nonsmokers. Among smokers, the lung cancer mortality ratio was 3.85 for men and 2.44 for women as compared to nonsmokers ($P<0.001$). Dose-response relationships were demonstrated for the number of cigarettes smoked per day and the age at initiation of smoking (figs. 1 and 2). These mortality ratios are considerably lower than those reported for the United States, Canada, and Great Britain, and may reflect a lower average number of cigarettes smoked a day, an older age at initiation of smoking, or reduced inhalation of cigarette smoke among the Japanese. In spite of these differences, the overall results of this study, including the dose-response relationships, are similar to the results of all the other major

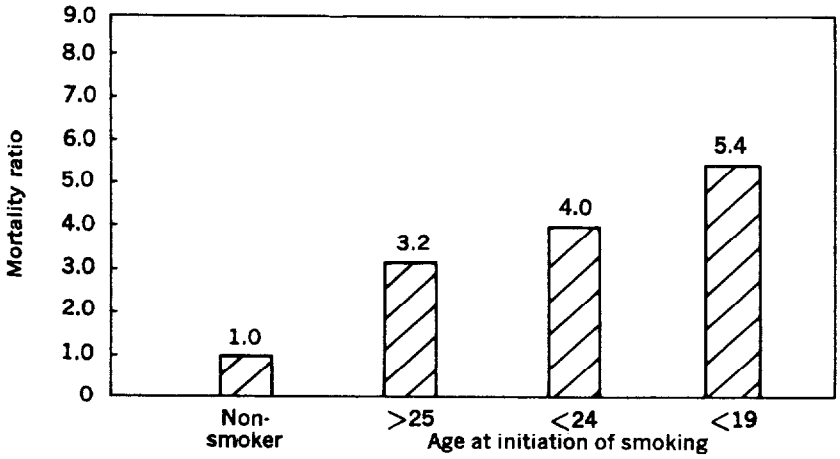
epidemiological investigations. Thus, the reliability and accuracy of the methods of population selection and analysis used in previous studies based on population samples, and the conclusion that cigarette smoking is the major cause of lung cancer are again confirmed.

Figure 1.—Standardized lung cancer mortality ratios of Japanese by number of cigarettes smoked (1966–1970).



SOURCE: Hirayama, T. (37).

Figure 2.—Lung cancer mortality ratios of Japanese by age at initiation of cigarette smoking (1966–1970).



SOURCE: Hirayama, T. (37).

TABLE 1.—*Age-standardized lung cancer death rates of British physicians and the population of England and Wales at various time periods*

Lung cancer standardized death rate per 1,000 men per year in—						
	Doctors			England and Wales		
Years	1953–57	1957–61	1961–65	1954–57	1958–61	1962–65
Death rate per 1,000	1.10	0.85	0.83	1.49	1.71	1.88

Source: Doll, R., Pike, M. C. (*22*).

Kennedy (*45*) studied primary lung cancer in 29 men and 11 women diagnosed before the age of 40 and found a strong association between cigarette smoking and the development of this disease.

Boucot, et al. (*11*) further characterized the 121 cases of lung cancer detected in the population of the Philadelphia pulmonary neoplasm research project. The risk of developing lung cancer increased with age, was higher in nonwhites than in whites, and increased sharply with increased cigarette consumption.

The relationship between cigarette smoking and lung cancer was investigated in a retrospective study by Ferrara (*25*) in La Plata, Argentina. The smoking habits of 144 lung cancer patients were contrasted with those of 386 controls. A dose-response relationship was found between cigarette usage measured by the number of cigarettes smoked per day and the duration of smoking and the risk of developing lung cancer.

A high incidence of lung cancer is reported from the island of Jersey in the Channel Isles compared to England and Wales. The island has no heavy industry and only minimal levels of air pollution. Cragg (*16*) studied 144 patients who developed lung cancer on Jersey during a 4-year study period. Only three nonsmokers were found among the 113 patients for whom histories were available.

Fingerland, et al. (*26*) determined the prevalence of lung cancer and certain other diseases in an autopsy series of 1,338 adults in Czechoslovakia. Some 198 cases of primary lung cancer were identified. In the autopsy population, 1.4 percent of the nonsmokers, 14.1 percent of those smoking less than 200,000 lifetime cigarettes, and 33.3 percent of those smoking more than 500,000 lifetime cigarettes had lung cancer.

Rickard and Sampson (*71*) studied 94 Negro patients with lung cancer in Washington, D.C., and found that 57 (92 percent) of 63 patients whose smoking history was available were regular smokers.

Epidemiological studies conducted in Italy (*10*), Sweden (*48*), Poland (*46*), Russia (*42*), Cuba (*73*), Mexico (*13*), and the Netherlands (*98*) demonstrate an association between cigarette smoking and lung cancer.

Berg, et al. (*5*) examined the incidence of recurrent primary cancers following initial primary cancers of the respiratory and upper digestive systems in New York. During 23,802 man-years of observation in 9,415 patients with an initial squamous cell cancer, 518 second cancers developed at other sites. Patients whose first primary cancer was in the lung had an observed to expected relative risk ratio of 5.7 ($P<0.05$) for subsequent cancers of the respiratory or upper GI system. Patients with the first cancer in the oral cavity or larynx frequently developed a second cancer in the lung. Medical records confirmed long smoking histories among almost all of these patients who developed second cancers.

Cancer of the lung, oral cavity, larynx, and esophagus were reported by Schmidt and De Lint (*79*) to be common causes of death among 6,578 men and women who had received treatment for alcoholism in Toronto. The authors attributed this finding to the strong association that exists between alcohol and tobacco use and not to the effect of alcohol alone.

Carcinoma of the trachea is a relatively rare condition with only about 400 cases having been reported in the literature. In a study of 41 patients with carcinoma of the trachea, Hajdu, et al. (*31*) found an apparent association between cigarette smoking and the development of epidermoid cancers of this structure.

An association between cigarette smoking and the development of bronchiolo-alveolar carcinoma in 74 patients was described by Delarue, et al. (*18*).

Ex-smokers

Those who stop smoking experience a decline in the risk of developing lung cancer relative to continuing smokers. Doll and Pike (*22*) conducted a study of the smoking habits and causes of death of 40,000 British physicians. Smoking habits were surveyed in 1951, 1957, and 1966. During the study period, more than 3,500 physicians became ex-smokers. The age-standardized percentage of ex-smokers among physicians 35 to 64 years of age rose from 18.1 percent in 1951 to 26.5 percent in 1957 and 29.5 percent in 1966. Concurrently, the percentage of physicians smoking cigarettes fell from 44.1 percent to 22.0 percent, while over the same period estimates of the per capita cigarette consumption for the adult male population in the United Kingdom suggested a slight increase in cigarette consumption. Over this 15-year period, the mortality from lung cancer among physicians dropped considerably while lung cancer death rates among the male population in England and Wales increased to some extent (table 1). Although cer-

tain limitations apply to the interpretations derived from secular data, analysis of the study design and the magnitude of the results indicate that this study constitutes important evidence of some of the benefits that result from the cessation of cigarette smoking.

Uranium Mining and Exposure to Radioactivity

Epidemiological evidence supported by autopsy studies has established that airborne radiation, particularly in synergistic combination with cigarette smoking, is the major cause of the excess of respiratory cancers among uranium miners.

Lundin, et al. (*53*) considered quantitative and temporal aspects of radon daughter exposure and respiratory cancer in a report from the Epidemiological Study of United States Uranium Miners. They observed a statistically significant excess of respiratory cancer among white uranium miners at each cumulative radiation exposure category down to and including 120–359 WLM (working level months). The authors noted that although cigarette smoking alone entailed a risk of the development of cancer of the respiratory tract in miners just as it does in nonminers, cigarette smoking in combination with radon daughter exposure appeared to result in an even greater risk.

Several authors (*30*, *44*, *63*, *84*, *104*) continue to report the presence of polonium-210 or one of the thorium isotopes in tobacco leaf, tobacco smoke, or the lungs of smokers.

Air Pollution

Data standardized for cigarette smoking indicate the existence of an urban factor in the development of lung cancer; it is likely that air pollution, frequently part of the city environment, is a component of the urban factor.

The National Academy of Sciences published a review (*61*) of the biological effects of atmospheric pollution by particulate polycyclic organic matter. Detailed epidemiological, experimental, physical, and chemical data were reviewed. It was concluded that air pollution, as commonly found in urban settings, was found to be associated with increased lung cancer mortality in cities. An examination of the data presented, however, indicates that cigarette smoking is, in most cases, the overriding factor in the development of lung cancer. Polycyclic hydrocarbons and related compounds which are known to cause cancer of the lung and other organs in experimental animals were found to

be present in relatively high concentrations in cigarette smoke, in large quantities in the air of industries in which workers have high-lung cancer rates, and also in the air of urban communities.

Sterling and Pollack (*86*) reviewed the effects of air pollution on death rates from lung cancer. They suggested that particles resulting from the combustion of organic fuels may be more strongly related to the incidence of lung cancer in the population than cigarette smoking. The cumulated epidemiological data regarding cigarette smoking and lung cancer were not considered by the authors in this report.

Asbestos

Cigarette smoking asbestos workers have markedly elevated lung cancer death rates compared to nonsmoking asbestos workers. Berry (*6*) examined the combined effect of asbestos exposure and smoking on mortality from lung cancer among 1,300 male and 480 female asbestos factory workers over a 10-year period. There was no significant increase in lung cancer mortality among smoking or nonsmoking workers with a low-to-moderate exposure to asbestos. However, among smokers who had heavy exposure to asbestos, 32 lung cancer deaths occurred among 663 men (9.9 expected), and there were 18 deaths among 292 women (1.4 expected). This confirms the greatly increased risk of developing lung cancer among asbestos workers who smoke cigarettes.

Autopsy and Cytological Studies

The respiratory tract of cigarette smokers examined at autopsy frequently demonstrates epithelial changes considered to be precursors of bronchogenic carcinoma. Such changes include squamous metaplasia, atypical squamous metaplasia, and carcinoma in situ. Herrold (*35*) studied histologic types of primary lung cancer in U.S. veterans who were subjects of the Dorn study. Of a total of 2,241 white male veterans who died of lung cancer over an 8-year period, histologic material was available for review in 1,477 patients. Histologic types were grouped according to the Kreyberg classification of Groups I and II tumors. Group I tumors, epidermoid and oat-cell carcinomas, were present in 27.3 percent of the 55 nonsmokers and were present in 57.8 percent of the 472 "current smokers of cigarettes only." The difference was statistically significant ($P<0.001$), confirming the strong association between cigarette smoking and Kreyberg Group I tumors.

Auerbach et al. (*2*) examined epithelial changes in the bronchial tree of 456 men and 302 women who had died of a cancer other than lung cancer. There were 72 ex-smokers among the men, all of whom had smoked for 10 years or more but had quit smoking for at least 5 years prior to death. Atypical cells were present in 93.2 percent of the current smokers, 6.0 percent of the ex-smokers, and 1.2 percent of the nonsmokers. Areas of epithelium composed entirely of atypical cells devoid of cilia were found in the bronchial tree of 8 percent of the current smokers, 0.2 percent of the ex-smokers, and none of the nonsmokers. Unusual cells with disintegrating or fading nuclei were found exclusively in 15 percent of the ex-smokers.

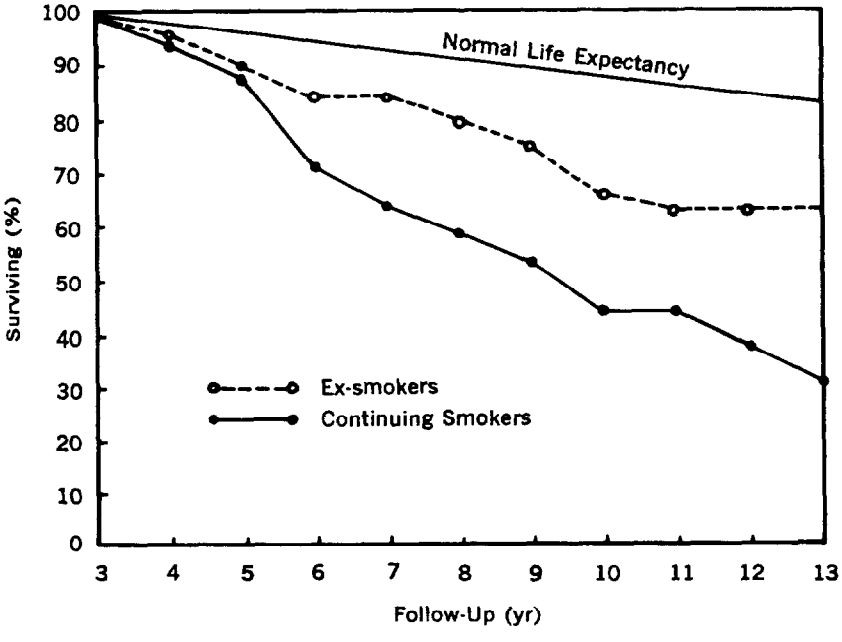
The prevalence of atypical cells (hyperplastic and metaplastic) in the sputum of 122 male and 128 female workers was examined by Robbins (*72*). These smokers, all under the age of 19, were matched with a control group drawn from a population of college students. Atypical cells were found in 14 percent of the smokers and 5 percent of the nonsmokers.

Oral Cancer

Data from the large Japanese prospective study by Hirayama (*37*) indicate that mortality rates from cancer of the oral cavity among males are higher in smokers than nonsmokers. A dose-response relationship was demonstrated for the age at initiation of smoking. The standardized mortality ratio among cigarette smokers was 10.0 for men ($P<0.001$) and 1.22 for women compared to nonsmokers. These ratios are not stable due to the few deaths that occurred from oral cancer in this study.

Certain relationships between cigarette smoking and cancer of the oral cavity, pharynx, and larynx were investigated by Moore (*59*). Over a 15-year period, 1,000 patients with invasive squamous carcinoma at these sites were treated in Kentucky. Of these patients, 203 had a history of cigarette smoking and had had no recurrence of cancer for a period of 3 years or more. This group was further divided on the basis of current smoking habits. Of the 122 who continued to smoke, 48 (40 percent) eventually developed a second cancer at these sites, whereas only five (6 percent) of the 81 who stopped smoking developed a second malignancy. This sixfold difference is statistically significant ($P<0.001$). The survival curves for these two groups are presented in figure 3.

Figure 3.—The survival of ex-smokers and continuing smokers who were treated for a primary cancer of the oral cavity, pharynx, or larynx.



SOURCE: Moore, C. (59).

Martinez (*57*) studied the relationship between smoking in various forms and cancer of the oral cavity in a retrospective study of 153 patients with this disease. Dose-response relationships were demonstrated for the amount smoked; the amount of alcohol consumed, and the development of cancer of the oral cavity.

Tyldesley (*90*) examined the prevalence of leukoplakia among 402 English coal miners of whom 280 smoked and chewed tobacco. Tobacco chewing was commonly found to be a substitute for smoking in underground conditions where smoking was impossible. Leukoplakia was found in 3.6 percent of the chewers, whereas no leukoplakia was found among the nonchewers.

Nelson and Ship (*62*) determined the relative influence of eight variable factors on the development of oral cancer in relation to age at the onset of disease in a population of 191 patients with a confirmed diagnosis of a primary squamous cell carcinoma of the oral cavity. The factors considered included age, sex, race, consumption of alcohol and tobacco, certain systemic diseases, and oral trauma. The prevalence of heavy tobacco use was more common among the younger patients. While 91 percent of the cancer patients under the age of 45 smoked more than 20 cigarettes a day, only 59 percent of the patients over 65 smoked this heavily.